DMAD (0.60 mmol) in CH_2Cl_2 (4 mL) was refluxed for 4 h. Chromatography of the reaction mixture gave 4,5,6,7-tetrahydro-2,3-bis(methoxycarbonyl)-4-(diphenylmethylene)-5,7-dioxo-6-tolylpyrazolo[1,5-*c*]pyrimidine (**24c**) (100%). Recrystallization of **24c** from CH_2Cl_2/pentane yielded orange-yellow needles: mp 277.5–279.0 °C; NMR δ 2.33 (s, 3 H), 3.55 (s, 3 H), 3.88 (s, 3 H), 6.98–7.40 (m, 14 H); IR (KBr) 1763, 1730, 1710 cm^{-1}; UV λ_{max} (MeOH) 238 (shoulder, ε 27 900), 387.4 (ε 10 400). Anal. Calcd for $C_{30}H_{23}N_3O_6 \cdot CH_2Cl_2$: C, 61.39; H, 4.16; N, 6.92. Found: C, 61.77; H, 4.27; N, 6.99.

Reaction of 4,6-Dihydro-3,3-dimethyl-4,6-dioxo-5-tolyl-3*H*-pyrrolo[3,4-*c*]pyrazole (19a) with Methanol. A solution of **19a** (1.00 mmol), methanol (4.00 mmol), and triethylamine (1.00 mmol) in CH_2Cl_2 (3 mL) was stirred for 1 day at room temperature. The reaction mixture was dissolved in CH_2Cl_2. The solution was washed with water and then dried over anhydrous magnesium sulfate. After evaporation of the solution, the residue was chromatographed over silica gel using benzene as eluent. Elution gave 3,3-dimethyl-4-(methoxycarbonyl)-5-(tolylcarbamoyl)-3*H*-pyrazole (**32**) (41%). Recrystallization of **32** from CH_2Cl_2/pentane yielded yellow needles: mp 171.5–172.5 °C; NMR δ 1.73 (s, 6 H), 2.32 (s, 3 H), 4.13 (s, 3 H), 7.13 (d, 2 H, J = 8.4 Hz), 7.55 (d, 2 H, J = 8.4 Hz), 11.38 (br s, 1 H); IR (KBr) 3261, 3123, 3077, 1697, 1664, 1620, 1591 cm^{-1}. Anal. Calcd for $C_{15}H_{17}N_3O_3$: C, 62.70; H, 5.96; N, 14.63. Found: C, 62.60; H, 5.95; N, 14.54. Further elution gave 3,3-dimethyl-5-(methoxycarbonyl)-4-(tolylcarbamoyl)-3*H*-pyrazole (**33**) (18%) as a yellow oil: NMR δ 1.59 (s, 6 H), 2.33 (s, 3 H), 3.94 (s, 3 H), 7.12 (d, 2 H, J = 8.4 Hz), 7.55 (d, 2 H, J = 8.4 Hz), 9.41 (br s, 1 H); IR (KBr) 3307, 3127, 3031, 1728, 1676, 1631, 1610 cm^{-1}.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture.

Regiospecific Alkylation of 3-Substituted-2-cyclohexen-1-ones. Synthesis and Conformational Analysis of 6-(Carbethoxymethyl)-3-substituted-2-cyclohexen-1-ones

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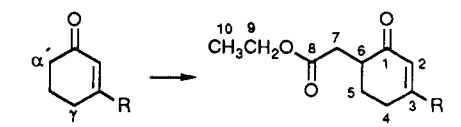
Received February 24, 1989

The reaction of 3-substituted-2-cyclohexen-1-ones **1–5** with lithium diisopropylamide in tetrahydrofuran, followed by ethyl bromoacetate, generated 6-(carbethoxymethyl)-3-substituted-2-cyclohexen-1-ones **6–10** in a 55–88% yield, regardless of the stoichiometry of the base (LDA) and cyclohexenone used in the reaction, provided that the temperature of the reaction was maintained at or below −50 °C. The use of dipolar aprotic solvents (e.g., HMPA and DMPU) with THF afforded no additional advantage in the reaction; however, with diethyl ether as the solvent no reaction occurred. Alkylation reactions involving ethyl bromoacetate or ethyl iodoacetate gave similar yields, but no alkylation product was obtained when ethyl chloroacetate was used. The use of lithium diisopropylamide or lithium bis(trimethylsilyl)amide at low temperature resulted in alkylation of 3-substituted-2-cyclohexen-1-ones only at the 6-position. The use of 2D NMR has allowed the complete assignment of the ^1H and ^{13}C NMR data. As a result, the dominant solution conformation for derivatives **6–10** is that having the 6-alkyl substituent in the equatorial orientation.

The regiospecific α′-alkylation of 3-alkoxy-2-cyclohexen-1-one and substituted 2-cyclohexen-1-ones was independently reported in 1973 by Stork and Danheiser and Lee et al., respectively.[1] Although many synthetic intermediates have been synthesized by this methodology, very few comparative reaction data are available.[2] In 1981, Chen et al. found that deprotonation of 3-ethoxy-2-cyclohexen-1-one, with excess lithium diisopropylamide (LDA) or lithium bis(trimethylsilyl)amide (LBTSA) in tetrahydrofuran (THF) at −78 °C, led to the formation of the α′-dienolate;[3] however, under no conditions was the γ-dienolate formed. Selective formation of the α′- or γ-dienolate of 3-(dimethylamino)-2-cyclohexen-1-one[3] and 2-methyl-3-pyrrolidinyl-2-cyclohexen-1-one[4] was dependent on the exact experimental conditions and lithium amide base employed.

A need for a variety of 6-(carbethoxymethyl)-3-substituted-2-cyclohexen-1-one derivatives (Scheme I) and a lack of comparative reaction data stimulated us to investigate the effect that variation in solvent, electrophile, stoichiometry, temperature, and lithium amide base have on the regiospecific alkylation of various 3-substituted-2-cyclohexen-1-ones. In this report we also describe a detailed NMR investigation and resulting conformational analysis of the 6-(carbethoxymethyl)-3-substituted-2-cyclohexen-1-ones.

Scheme I



1, R = H
2, R = CH_3
3, R = $CH_2(CH_2)_2CH_3$
4, R = Ph
5, R = OCH_2CH_3

6, R = H
7, R = CH_3
8, R = $CH_2(CH_2)_2CH_3$
9, R = Ph
10, R = OCH_2CH_3

A procedure similar to that described in the literature[5] was used to examine the effect of solvent on this reaction. Briefly, this involved the slow addition of 2-cyclohexen-1-one (**1**) to excess lithium diisopropylamide (LDA) at low temperature, followed by the slow addition of ethyl iodo-

(1) (a) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775. (b) Lee, A. R.; McAndrews, C.; Patel, K.; Reusch, W. *Tetrahedron Lett.* **1973**, *12*, 965.

(2) (a) Audenaert, F.; Keukeleire, D. D.; Vandewalle, M. *Tetrahedron* **1987**, *43*, 5593. (b) Gesson, J. P.; Jacquesy, J. C.; Renoux, B. *Tetrahedron Lett.* **1986**, *27*, 4461. (c) Majetich, G.; Behnke, M.; Hull, K. *J. Org. Chem.* **1985**, *50*, 3615.

(3) Chen, Y. L.; Mariano, P. S.; Little, G. M.; O'Brien, D.; Huesmann, P. L. *J. Org. Chem.* **1981**, *46*, 4643.

(4) Telschow, J. E.; Reusch, W. *J. Org. Chem.* **1975**, *40*, 862.

(5) Wege, P. M.; Clark, R. D.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 5144.

0022-3263/89/1954-5919$01.50/0

Table I. Regiospecific Alkylation of 3-Substituted-2-cyclohexen-1-ones

substrate	conditions[a]	product	yield,[b] %
1	A	6	71
	B		65
	C		70
2	A	7	88
	B		86
	C		75
3	A	8	83
	B		72
4	A	9	87
	B		71
	C		79
5	A	10	56
	B		55

[a] Conditions: (A) Simplified procedure utilizing excess LDA at low temperature, method A. (B) Simplified procedure utilizing excess cyclohexenone at low temperature, method B. (C) Simplified procedure utilizing excess LBTSA at low temperature, method C. The electrophile is ethyl bromoacetate for methods A, B, and C. [b] Yields are for isolated, purified material.

acetate. The solvents examined included tetrahydrofuran (THF), a mixture of hexamethylphosphoramide (HMPA) and tetrahydrofuran (1/12 ratio), and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU)[6] mixed with tetrahydrofuran (1/5 ratio). The yield of alkylation product **6** ranged from 63% to 67%. When diethyl ether was used as a sole solvent, the heterogeneous mixture did not yield any alkylation product (e.g., **6**). Thus, homogeneous reaction conditions appear necessary for these alkylations to be successful. Additionally, no further advantage was observed when polar aprotic solvents such as HMPA or DMPU were used as cosolvents in the reaction.

The electrophiles ethyl iodoacetate (2 equiv), ethyl bromoacetate (2 equiv), and ethyl chloroacetate (2 equiv) were reacted with 3-methyl-2-cyclohexen-1-one (**2**) under reaction conditions similar to those used in the solvent study. With THF as the solvent the alkylated product **7** was isolated in a 97%, 90%, and 0% yield, respectively. In the case of ethyl chloroacetate, only starting material was observed. The failure of ethyl chloroacetate to effect alkylation may result from its greater acidity, compared to the other ethyl α-haloacetates. This greater acidity may allow lithium–hydrogen exchange to occur between the lithium dienolate of 3-methyl-2-cyclohexen-1-one and ethyl chloroacetate. However, the reaction conditions must be unfavorable for a Darzens reaction to occur since only starting material was observed.[7]

The importance of the stoichiometry between the base and cyclohexenone was investigated at low temperature.[8] The alkylation of 3-methyl-2-cyclohexen-1-one (**2**, 20% excess) with ethyl iodoacetate at −78 °C gave an 88% yield of **7**. Since a similar yield of **7** was obtained, regardless of the stoichiometry between the base and the cyclohexenone, it can be concluded that the α'-dienolate is formed and is stable at low temperature.

As a result of establishing the importance of conducting the reaction at a low temperature to produce the 6-alkylated product, a simplified experimental procedure has been developed. This reaction involved the addition of the cyclohexenone derivative to the LDA solution[9] (−78 °C),

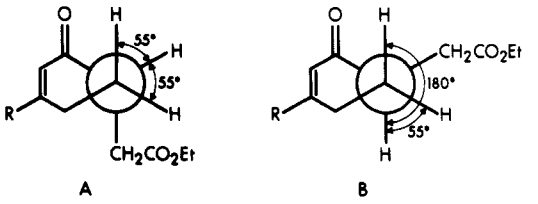


Figure 1. Newman projections of derivatives **6–10**.

followed by addition of ethyl bromoacetate, at a rate that maintained a reaction temperature at or below −50 °C. Quenching at −78 °C and purification gave the desired 6-alkylated-3-substituted-2-cyclohexen-1-one derivatives **6–10** in good yield (56%–88%, Table I, method A).[10] Additionally, this procedure significantly reduced the experimental manipulations needed and overall reaction time.

The simplified reaction procedure was conducted as described above using an excess of the 3-substituted-2-cyclohexen-1-one to further examine the importance of maintaining a low reaction temperature. A comparison of the results from this experiment (Table I, method B) and when excess LDA was used (Table I, method A) revealed no significant difference in the yield of the 6-alkylated products **6–10**. If, however, ethyl bromoacetate was added to the reaction at 0 °C, a 30% yield of **7** was obtained, compared to an 86% yield if ethyl bromoacetate was added at −78 °C. Thus, the reaction must be conducted at a low temperature (<−50 °C) to maximize the amount of the 6-alkylated product.

The alkylation of 3-substituted-2-cyclohexen-1-ones was examined with lithium bis(trimethylsilyl)amide (LBTSA) to determine if selective formation of the 4-alkylated product would result, as is the case for 3-(dimethylamino)-2-cyclohexen-1-one.[3] The simplified reaction conditions using excess base were followed with one minor change, the dienolate was stirred for 30 minutes at −78 °C before the electrophile (ethyl bromoacetate) was added, to simulate the reaction conditions used by Chen et al. with 3-(dimethylamino)-2-cyclohexen-1-one.[3] In this study, only the 6-alkylated product was obtained (Table I, method C) in yields very similar to those obtained when LDA was used. These results indicate that the 3-amino-2-cyclohexen-1-one derivatives behave differently than the other 3-substituted-2-cyclohexen-1-ones.

The structural assignment of the 6-(carbethoxymethyl)-3-substituted-2-cyclohexen-1-ones (**6–10**) was completed using 2D NMR COSY and HETCOR experiments. With these data, the stereochemistry of the 6-alkyl substituent was ascertained by determining the coupling constants between protons H-5 and H-6.[11] Inspection of the Dreiding model for derivatives **6–10**, assuming a half-chair conformation, showed that the dihedral angles formed by H-6, C-6, C-5, H-5α, and H-5β are approximately equal to 55° when the 6-alkyl substituent is in the axial position (Figure 1A) and 180 and 55° (Figure 1B) when the 6-alkyl substituent is in the equatorial position. By the Karplus relationship,[12] either two small (4–5 Hz) or a large (10–12 Hz) and a small (4–5 Hz) vicinal coupling

(6) Mukhopadhyan, T.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 385.
(7) This point was kindly suggested by a referee.
(8) (a) The standard procedure would supposedly minimize side reactions (e.g., proton transfer[3] and dimerization of the cyclohexenone[8b]): (b) Buchi, G.; Hansen, J. H.; Knutson, D.; Koller, E. *J. Am. Chem. Soc.* **1958**, *80*, 5517.
(9) Podraza, K. F.; Bassfield, R. L. *J. Org. Chem.* **1988**, *53*, 2643.
(10) (a) This new procedure generated yields as good as or better than those reported in the literature.[10b,c] (b) Williams, J. R.; Cleary, T. P. *J. Chem. Soc. Chem. Comm.* **1982**, 626. (c) Heathcock, C. H. *Int. Congr. Essent. Oils* **1974**, 160.
(11) (a) Molecules such as 2-cyclohexen-1-one derivatives are conformationally mobile; therefore, a weighted average of the interchanging conformers is observed in the NMR spectrum.[11b] (b) Torri, J.; Azzaro, M. *Bull. Soc. Chim. Fr.* **1974**, 1633.
(12) (a) Karplus, M. *J. Chem. Phys.* **1958**, *30*, 11. (b) Karplus, M. *J. Am. Chem. Soc.* **1963**, *85*, 2870.

constant would result. The vicinal coupling for $J(5\beta,6)$ and $J(5\alpha,6)$ of derivative **7** was 12.5 and 5.2 Hz, respectively.[13] A similar coupling pattern was observed throughout the series of compounds; however, for compounds **6** and **9**, the H-6 signal was partially overlapped, making the measurements difficult. The NMR data suggest that the preferred solution conformation for compounds **6–10** is with the 6-alkyl substituent in the equatorial orientation.

In conclusion, we have established that the α'-dienolate of 3-substituted-2-cyclohexen-1-ones **1–5** rapidly form at low temperature (<–50 °C) regardless of the stoichiometry between the base (LDA) and the 3-substituted-2-cyclohexen-1-one in tetrahydrofuran. As a result, a simplified procedure has been developed to synthesize 6-alkylated-3-substituted-2-cyclohexen-1-ones in good yield.

Experimental Section

Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Infrared spectra were recorded on a Perkin-Elmer 1320 spectrophotometer. The carbon and proton nuclear magnetic resonance (NMR) spectra were recorded on a Varian XL-300 or XL-400 spectrometer. The chemical shifts and coupling constants (J) are reported in δ and hertz, respectively. Radial chromatography was conducted with a Harrison Research Model 7924 chromatotron utilizing a 4-mm plate with silica gel 60 GF 254 (EM Labs) as the adsorbent. All the reactions were conducted under an argon atmosphere.

General Procedure Utilized in the Solvent Study. 6-(Carbethoxymethyl)-2-cyclohexen-1-one (6), Solvent 1. To a solution of 3.46 g (34.3 mmol) of diisopropylamine in 50 mL of THF at –78 °C was added 13.74 mL (34.3 mmol) of 2.5 M *n*-butyllithium in hexane, and the solution was stirred for 15 min.[9] To the solution of lithium diisopropylamide (LDA) was added, over 30 min, 3.0 g (31.2 mmol) of 2-cyclohexen-1-one in 10 mL of THF. The solution was stirred for 30 min at –78 °C followed by the addition, over 15 min, of a solution of 13.4 g (62.4 mmol) of ethyl iodoacetate in 10 mL of THF. The solution was stirred for 2.5 h at –78 °C. The solution was diluted with ether and quenched with saturated aqueous NH_4Cl. The mixture was allowed to warm to approximately 0 °C, and the aqueous layer was extracted with ether. The combined organic extracts were washed with saturated aqueous NH_4Cl and saturated NaCl, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The oil was purified by vacuum distillation to yield 3.69 g (65%) of **6**: bp 77–80 °C/0.01 mmHg; IR (film) 1720, 1665, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.00–6.95 (m, 1 H, H-3), 6.03 (d, J = 10.2 Hz, 1 H, H-2), 4.16 (quartet, J = 7.2 Hz, 2 H, H-9), 2.95–2.81 (m, 2 H, H-6, H-7), 2.55–2.35 (m, 2 H, H-4), 2.32–2.20 (m, 1 H, H-7), 2.18–2.08 (m, 1 H, H-5), 1.90–1.74 (m, 1 H, H-5), 1.27 (t, J = 7.2 Hz, 3 H, H-10); ^{13}C ($CDCl_3$) δ 199.39 (C-1), 172.37 (C-8), 150.15 (C-3), 129.14 (C-2), 60.42 (C-9), 43.67 (C-6), 34.57 (C-7), 28.69 (C-5), 25.98 (C-4), 14.22 (C-10). Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.60; H, 7.77.

Solvent 2. The reaction of 2-cyclohexen-1-one (1.0 g, 10.4 mmol) in 5 mL of THF and 1.8 mL of HMPA with LDA (11.5 mmol) followed by ethyl iodoacetate (4.45 g, 20.8 mmol) in 5 mL of THF at –78 °C was conducted in a fashion similar to that for solvent 1. After addition of the reagents the solution was stirred for 2 h at –78 °C and then 16 h at room temperature. Purification of the crude material yielded 1.27 g (67%) of **6**.

Solvent 3. The reaction of 2-cyclohexen-1-one (3.0 g, 31.2 mmol) in 10 mL of THF and 12 mL of DMPU with LDA (34.3 mmol) followed by ethyl iodoacetate (13.3 g, 62.4 mmol) in 10 mL of THF at –78 °C was conducted in a fashion similar to that for solvent 1. After addition of the reagents the solution was stirred for 2 h at –78 °C then allowed to warm to room temperature, and quenched. Purification of the crude material yielded 3.56 g (63%) of **6**.

Solvent 4. The reaction of 2-cyclohexen-1-one (1.0 g, 10.4 mmol) in 10 mL of anhydrous diethyl ether with LDA (11.5 mmol) followed by ethyl iodoacetate (2.22 g, 10.4 mmol) in 5 mL of ether at –78 °C was conducted in a fashion similar to that for solvent 2. The crude material was examined by TLC, and no alkylated product **6** was observed.

General Procedure Utilized in the Electrophile Study. 6-(Carbethoxymethyl)-3-methyl-2-cyclohexen-1-one (7), Electrophile 1. To a solution of LDA (29.9 mmol) at –78 °C was added, over 30 min, 3.0 g (27.2 mmol) of 3-methyl-2-cyclohexen-1-one in 10 mL of THF. The solution was stirred for 30 min at –78 °C followed by the addition, over 15 min, of a solution of 11.6 g (54.4 mmol) of ethyl iodoacetate in 10 mL of THF. The solution was stirred for 2.5 h at –78 °C. The solution was diluted with ether and quenched with saturated aqueous NH_4Cl followed by the normal isolation procedure. The crude material was purified by Kugelrohr distillation to yield 5.2 g (97%) of **7**:[10b] bp 45–90 °C/0.01 mmHg; IR (film) 1725, 1660, 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.88 (s, 1 H, H-2), 4.16 (quartet, J = 7.2 Hz, 2 H, H-9), 2.89 (dd, J = 5.4 Hz, 1 H, H-7), 2.81–2.70 (m, 1 H, H-6), 2.55–2.37 (m, 1 H, H-4), 2.33–2.20 (m, 2 H, H-4, H-7), 2.17–2.06 (m, 1 H, H-5), 1.96 (s, 3 H, H-11), 1.87–1.70 (m, 1 H, H-5), 1.27 (t, J = 7.2 Hz, 3 H, H-10); ^{13}C NMR ($CDCl_3$) δ 199.22 (C-1), 172.70 (C-8), 162.02 (C-3), 126.03 (C-2), 60.49 (C-9), 42.63 (C-6), 34.62 (C-7), 31.07 (C-4), 28.53 (C-5), 24.21 (C-11), 14.22 (C-10).

Electrophile 2. The reaction of 3-methyl-2-cyclohexen-1-one (3.0 g, 27.2 mmol) with LDA (29.9 mmol) and ethyl bromoacetate (9.1 g, 54.4 mmol) was conducted in a fashion similar to that for electrophile 1. Purification of the crude material yielded 4.80 g (90%) of **7**.

Electrophile 3. The reaction of 3-methyl-2-cyclohexen-1-one (3.0 g, 27.2 mmol) with LDA (29.9 mmol) and ethyl chloroacetate (6.7 g, 54.4 mmol) was conducted in a fashion similar to that for electrophile 1. The crude material obtained after the normal isolation procedure was examined by GC and found to contain only starting material.

General Procedure Utilized in the Excess Cyclohexenone Low-Temperature Study. To a solution of LDA (22.8 mmol) at –78 °C was added, over 30 min, 3.0 g (27.2 mmol) of 3-methyl-2-cyclohexen-1-one in 10 mL of THF. The solution was stirred for 30 min at –78 °C followed by the addition of 11.6 g (54.4 mmol) of ethyl iodoacetate in 10 mL of THF. The solution was stirred for 2.5 h at –78 °C. The mixture was diluted with ether and quenched with saturated aqueous NH_4Cl. The normal isolation and purification procedure was conducted to yield 3.75 g (88%) of **7**.

Simplified Procedure Utilized in the Excess LDA Low-Temperature Study. 6-(Carbethoxymethyl)-2-cyclohexen-1-one (6), Method A. To a solution of LDA[9] (34.3 mmol) at –78 °C was added 3.0 g (31.2 mmol) of 2-cyclohexen-1-one in 10 mL of THF at a rate that allowed a temperature at or below –50 °C to be maintained. The solution was stirred for 10 min, and then 6.25 g (37.4 mmol) of ethyl bromoacetate in 10 mL of THF was added at a rate that allowed a temperature at or below –50 °C to be maintained. The solution was stirred for 2 h at –78 °C, then diluted with ether, and quenched with saturated aqueous NH_4Cl. The mixture was allowed to warm to approximately 0 °C, and the aqueous layer was extracted with ether. The combined organic extracts were washed with saturated aqueous NH_4Cl and saturated NaCl, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The material was purified as previously described to yield 4.02 g (71%) of **6**.

6-(Carbethoxymethyl)-3-methyl-2-cyclohexen-1-one (7). The reaction of 3-methyl-2-cyclohexen-1-one (3.0 g, 27.2 mmol) with LDA (29.9 mmol) and ethyl bromoacetate (5.5 g, 32.7 mmol) was conducted in a fashion similar to that of method A. The crude material was purified by Kugelrohr distillation to yield 4.70 g (88%) of **7**.

6-(Carbethoxymethyl)-3-butyl-2-cyclohexen-1-one (8). The reaction of 3-butyl-2-cyclohexen-1-one[14a,c] (3.0 g, 19.7 mmol) with LDA (21.7 mmol) and ethyl bromoacetate (3.96 g, 23.6 mmol) was conducted in a fashion similar to that for method A. The crude material was purified by Kugelrohr distillation to yield 3.92 g (83%) of **8**: bp 80–105 °C/0.01 mmHg; IR (film) 1720, 1655, 1615

(13) Coupling constant data for **7**: $J_{H_{7\alpha,6}}$ = 7.8; $J_{H_{7\beta,6}}$ = 5.6; $J_{H_{5\alpha,\beta}}$ = –12.5; $J_{H_{7\alpha,\beta}}$ = –16.3.

(14) (a) Kraus, G. A.; Krolski, M. E. *Synth. Commun.* **1982**, *12*(7), 521. (b) Piers, E.; Cheng, K. F.; Nagakura, I. *Can. J. Chem.* **1982**, *60*, 1256. (c) Giersch, W.; Ohloff, G. Ger. Offen. 2,938,979, Apr 10, 1980; *Chem. Abstr.* 93:191915e.

cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.87 (s, 1 H, H-2), 4.16 (quartet, J = 7.2 Hz, 2 H, H-9), 2.90 (dd, J = 5.2 Hz, 1 H, H-7), 2.80–2.70 (m, 1 H, H-6), 2.50–2.16 (m, 5 H, H-4, H-7, H-11), 2.15–2.08 (m, 1 H, H-5), 1.83–1.70 (m, 1 H, H-5), 1.48 (quintet, J = 8.0 Hz, 2 H, H-12), 1.33 (sextet, J = 7.2 Hz, 2 H, H-13), 1.27 (t, J = 7.2 Hz, 3 H, H-10), 0.92 (t, J = 7.2 Hz, 3 H, H-14); ^{13}C NMR ($CDCl_3$) δ 199.43 (C-1), 172.69 (C-8), 166.04 (C-3), 124.95 (C-2), 60.46 (C-9), 42.97 (C-6), 37.53 (C-11), 34.66 (C-7), 29.75 (C-4), 29.09 (C-12), 28.68 (C-5), 22.34 (C-13), 14.22 (C-10), 13.85 (C-14). Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.55; H, 9.27.

6-(Carbethoxymethyl)-3-phenyl-2-cyclohexen-1-one (9). The reaction of 3-phenyl-2-cyclohexen-1-one[14a,b] (3.0 g, 17.4 mmol) with LDA (19.2 mmol) and ethyl bromoacetate (3.5 g, 20.9 mmol) was conducted in a fashion similar to that of method A. The crude material was purified by Kugelrohr distillation to yield 3.90 g (87%) of **9**: bp 100–130 °C/0.01 mmHg; IR (film) 1720, 1650, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.58–7.50 (m, 2 H, Ar protons), 7.47–7.38 (m, 3 H, Ar protons), 6.43 (s, 1 H, H-2), 4.18 (quartet, J = 7.2 Hz, 2 H, H-9), 3.00–2.75 (m, 4 H, H-4, H-6, H-7), 2.40–2.25 (m, 2 H, H-5, H-7), 2.03–1.80 (m, 1 H, H-5), 1.29 (t, J = 7.2 Hz, 3 H, H-10); ^{13}C NMR ($CDCl_3$) δ 199.39 (C-1), 172.50 (C-8), 159.06 (C-3), 138.39 (Ph), 130.01 (Ph), 129.97 (Ph), 128.84 (Ph), 128.74 (Ph), 126.03 (Ph), 124.56 (C-2), 60.49 (C-9), 42.89 (C-6), 34.61 (C-7), 28.64 (C-5), 28.06 (C-4), 14.22 (C-10). Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02. Found: C, 74.55; H, 7.12.

6-(Carbethoxymethyl)-3-ethoxy-2-cyclohexen-1-one (10). The reaction of 3-ethoxy-2-cyclohexen-1-one (3.0 g, 21.4 mmol) with LDA (23.5 mmol) and ethyl bromoacetate (4.3 g, 25.7 mmol) was conducted in a fashion similar to that of method A. The crude material was purified by flash chromatography on silica gel eluted with 10% to 40% ethyl acetate in hexane to yield 2.70 g (56%) of **10**:[10c] IR (film) 1720, 1655, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.35 (s, 1 H, H-2), 4.16 (quartet, J = 7.5 Hz, 2 H, H-9), 3.95–3.85 (m, 2 H, H-11), 2.93 (dd, J = 4.5 Hz, 1 H, H-7), 2.79–2.65 (m, 1 H, H-6), 2.63–2.50 (m, 1 H, H-4), 2.45–2.35 (m, 1 H, H-4), 2.27 (dd, J = 7.8 Hz, 1 H, H-7), 2.15–2.07 (m, 1 H, H-5), 1.87–1.70 (m, 1 H, H-5), 1.36 (t, J = 7.5 Hz, 3 H, H-12), 1.27 (t, J = 7.5 Hz, 3 H, H-10); ^{13}C NMR ($CDCl_3$) δ 198.96 (C-1), 177.53 (C-3), 172.72 (C-8), 101.99 (C-2), 64.38 (C-11), 60.44 (C-9), 42.33 (C-6), 34.79 (C-7), 29.03 (C-4), 27.15 (C-5), 14.23 (C-10), 14.15 (C-12).

Simplified Procedure Utilized in the Excess Cyclohexenone Low-Temperature Study, Method B. The reaction of 2-cyclohexen-1-one (3.0 g, 31.2 mmol) with LDA (25 mmol) and ethyl bromoacetate (5.21 g, 31.2 mmol) was conducted in a fashion similar to that of method A. The normal isolation and purification procedure yielded 3.70 g (65%) of **6**. In a similar fashion the other 3-substituted-2-cyclohexen-1-ones were examined under these conditions, and the yield of the alkylated product is shown in Table I.

Simplified Procedure Utilized in the Excess LBTSA Low-Temperature Study, Method C. The reaction of 2-cyclohexen-1-one (2.0 g, 20.8 mmol) with LBTSA (22.9 mmol) and ethyl bromoacetate (4.60 g, 27.5 mmol) was conducted in a fashion similar to that of method A, with the exception that the dienolate was stirred for 30 min at −78 °C before ethyl bromoacetate was added. The normal isolation and purification procedure yielded 2.65 g (70%) of **6**. In a similar fashion the other 3-substituted-2-cyclohexen-1-ones were examined under these conditions, and the yield of the alkylated product is shown in Table I.

Registry No. **1**, 930-68-7; **2**, 1193-18-6; **3**, 6301-49-1; **4**, 10345-87-6; **5**, 5323-87-5; **6**, 111248-50-1; **7**, 83108-31-0; **8**, 123540-67-0; **9**, 123540-68-1; **10**, 58775-57-8; ethyl iodoacetate, 623-48-3; ethyl bromoacetate, 105-36-2.

Does the Reaction of Cu^+ with H_2O_2 Give OH Radicals? A Study of Aromatic Hydroxylation

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Received May 30, 1989

The reaction of Cu^+ with H_2O_2 was studied by using the isomer distribution obtained with fluorobenzene, anisole, and nitrobenzene as a probe for OH radicals. The reaction with benzene in presence of 5×10^{-2} M Cu^{2+} gave a maximum yield of 69% phenol. The isomer distributions obtained with fluorobenzene, anisole, and nitrobenzene are almost identical with those obtained in the radiation-induced hydroxylation under similar conditions. In experiments with benzene and nitrobenzene we have shown that Cu^{3+} produced via Cu^{2+} + OH does not hydroxylate these aromatic compounds in neutral or weakly acidic solutions (pH 5.0–6.0). We therefore conclude that in the reaction of Cu^+ with H_2O_2 the OH radical is the major reactive species that reacts with aromatic compounds.

The Cu^+ autoxidation has been studied extensively[1,2] ever since the hydroxylating properties of the Cu^+–O_2 system were discovered.[3,4] Evidence for[4] and against[5] the intermediate formation of OH radicals has been presented.[6] Recently a group of Japanese workers[7] have examined the Cu^+–O_2-induced hydroxylation of benzene and concluded that the reaction proceeds via OH radicals. At the same time we published a paper[8] on the reaction of Cu^+–O_2 using DMSO as a OH radical probe, reaching the same conclusion as the Japanese workers. It was suggested by both groups that the H_2O_2 produced in the autoxidation reacts with Cu^+ to give OH radical in a Fenton-type reaction. There is considerable evidence for this reaction in the literature.[9-12] It is frequently quoted without any references. However, contrary evidence was presented by

(1) Zuberbühler, A. *Helv. Chim. Acta* **1970**, *53*, 473–485.
(2) Rainoni, G.; Zuberbühler, A. *Chimia* **1974**, *28*, 67–70.
(3) Udenfriend, S.; Clark, C. T.; Axelrod, J.; Brodie, B. B. *J. Biol. Chem.* **1954**, *208*, 731.
(4) Nofre, C.; Cier, A.; Lefier, A. *Bull. Soc. Chim. Fr.* **1962**, 530.
(5) Dearden, M. B.; Jefcoate, C. R.; Lindsay-Smith, J. R. *Advances in Chemistry Series*; Gould, R. F., Ed.; American Chemical Society: Washington, DC, 1968; Vol. 77, Part III, p 260, and references cited therein.
(6) For a discussion on the nature of the primary oxidants mediated by metal ions, see also: Walling, C. In *Oxidases and Related Redox Systems*; King, T. E., Mason, H. S., Morrison, M., Eds.; Pergamon Press, Oxford, 1982; pp 85–97.
(7) Ito, S.; Yamasaki, T.; Okada, H.; Okino, S.; Sasaki, K. *J. Chem. Soc., Perkin Trans. 2* **1988**, 285.
(8) Eberhardt, M. K.; Colina, R.; Soto, K. *J. Org. Chem.* **1988**, *53*, 1074.
(9) Que, B. G.; Downey, K. M.; So, A. G. *Biochemistry* **1980**, *19*, 5987.
(10) Buxton, G. V.; Green, J. C.; Sellers, R. M. *J. Chem. Soc., Dalton Trans.* **1976**, 2160.
(11) Czapski, G.; Aronovitch, J.; Samuni, A.; Chevion, M. *Oxyradicals and their Scavenger Systems*; Cohen, G., Greenwald, R. A., Eds. Elsevier: Amsterdam 1983; Vol. I: Molecular Aspects, p 111.
(12) Goldstein, S.; Czapski, G. *J. Am. Chem. Soc.* **1983**, *105*, 7276.

0022-3263/89/1954-5922$01.50/0